# Predictive value of transvaginal ultrasound score for detection of endometrial malignancy

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**Summary**

Purpose: The aim of this study was to assess the accuracy of transvaginal ultrasound in detecting endometrial malignancy in perimenopausal women. *Material and Methods:* The cross-sectional study included 100 perimenopausal women who had changes on the endometrium discovered through a regular ultrasound check-up and were referred to Clinic of Gynecology and Obstetrics "Narodni Front" in Belgrade during the period from September 1, 2012 to September 1, 2013. Transvaginal ultrasound was performed on each participant in the study. Parameters of the ultrasound examination composed a score system. *Result:* The results of regression analysis showed that this transvaginal ultrasound score have independent prognostic value for detection of endometrial malignancy. Score system showed that the value 8 had the best validity for the detection of endometrial malignity, with the sensitivity of 0.857 and specificity of 0.785. *Conclusion:* The collected transvaginal ultrasound sample had high predictive value for the discovery of malign changes on endometrium.

*Key words:* Ultrasound; Perimenopause; Endometrial carcinoma; Metrorrhagia; Endometrial hyperplasia; Endometrial polyps; Endometrial thickness.

## Introduction

Ultrasonography is a method that allows visualization of endometrium and recognition of its pathology, and is a painless and non-invasive method that requires minimal time for a check-up and is acceptable by the majority of women [1, 2]. A reduced production of estrogen in perimenopause causes endometrium atrophy, which gives a sonographic picture of a narrow and intermittent structure. The major ultrasonographic finding in females with pathological changes of endometrium is thickening of endometrium [2]. The results from numerous studies have confirmed that sensitivity for detection of pathological changes of endometrium according to the sonographic thickness is very low [3]. There are no reliable sonomorphologic criteria to distinguish findings between benign and malign changes on the endometrium. The most frequent benign conditions are: endometrial polyp or endometrial hyperplasia. For both of these changes the most frequent is a thickened endometrium of a homogenous appearance, unlike thickened endometrium of an inhomogeneous appearance that is found in atypical hyperplasia and endometrial carcinoma [4]. Among females between 45-55 years of age, the most frequent signs are disorders of menstrual cycle as an absence of menstruation or irregular bleeding from the uterus [5]. In this group of patients, ultrasound most frequently shows thickness of endometrium, endometrial polyp or there is a suspicion of a malign process in the endometrium [6]. An early diagnosis is an imperative for the prognosis of the patients suffering from endometrium carcinoma. To the best of the present authors' knowledge, there is no sufficient valid screening test for detection of endometrial malignancy**.** The aim of this study was to establish transvaginal ultrasound score as well as to investigate its predictive value in detection of endometrial malignancy.

## Materials and Methods

The survey was designed as a type of cross-sectional study. It was performed from September 1, 2012 to September 1, 2013, in the Clinic of Gynecology and Obstetrics "Narodni Front" in Belgrade, a referral centre for gynecology in Serbia. The study included 100 perimenopausal women, that had changes on the endometrium, discovered through a regular ultrasound check-up or the patients were directed to the clinic due to irregular bleeding from the uterus. The exclusion criteria were: previously confirmed malignant disease, myoma of the uterus, any adnexal pathology, and hematological disorder. All the patients had regular colposcopic and cytological finding in the last six months. Transvaginal ultrasound was performed on each participant in the study. Check-ups were done using ultrasonic apparatus with a five-MHz transvaginal probe. In each patient the uterine cavity was checked in the sagittal and the transversal planes.

The ultrasound examination was described by a selected group of parameters that composed a score according to which state the endometrium was evaluated. This score included the following
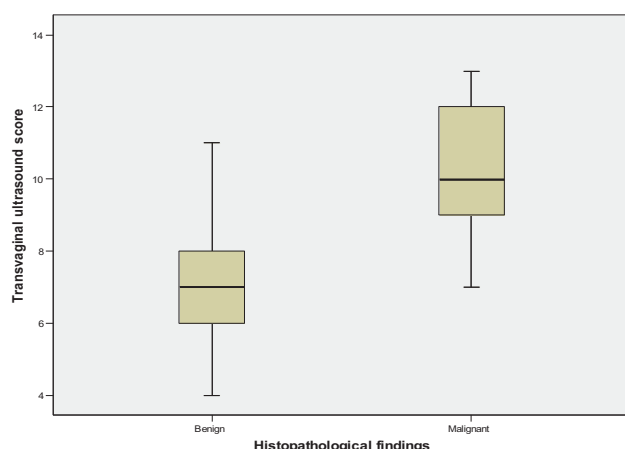
Figure 1. — Values of transvaginal ultrasound score according to the histopathological findings.

Table 1. — *Sensitivity and specificity values of transvaginal ultrasound score for each possible cut-off between benign and malignant histopathological findings.*

| Positive if greater than or equal to (a) | Sensitivity | 1 - Specificity |
|---|---|---|
| 3.00 | 1.000 | 1.000 |
| 4.50 | 1.000 | 0.911 |
| 5.50 | 1.000 | 0.772 |
| 6.50 | 1.000 | 0.544 |
| 7.50 | 0.905 | 0.380 |
| 8.00 | 0.857 | 0.215 |
| 9.50 | 0.667 | 0.101 |
| 10.50 | 0.476 | 0.038 |
| 11.50 | 0.333 | 0.000 |
| 12.50 | 0.143 | 0.000 |
| 14.00 | 0.000 | 0.000 |

parameters: thickness of endometrium (up to five mm = 0, from five to eight mm = 1, > eight mm = 2), echogenicity of the endometrium compared to the myometrium: normal echogenicity = 0, hyperechogenous = 1, hypoechogenous = 2 , the border of the endometrium towards the myometrium - subendometrial hypoechogenous zone (whole = 0. intermittent = 1), homogeneity of the texture of the endometrium (homogenous = 1. inhomogeneous = 2), presence of the coloured signals in the endometrium (present = 2. absent = 1), index of resistance in newly-formed blood vessels of the endometrium (> 0.4 = 1. < 0.40 = 2), volume of the endometrium by an ultrasound check-up (< 13 ml = 1. > 13 ml = 2). All females in the present study had fractional explorative curettage and the obtained material was examined histopathologically. Before the intervention, in order to exclude the presence of malign changes on cervix, a cytological and colposcopic check-up was performed. Anaesthesia was mainly intravenous.

The primary analysis involved descriptive statistics summary for estimating demographic and clinical characteristics of the study participants. The differences between transvaginal ultrasound score among perimenopausal females with and without endometrial malignancy were assessed by using $t$- test. Independent predictors of endometrial malignancy were identified using a series of logistic regression models based on heterogeneous risk factors with potential confounding effects. All potential covariates were first analyzed in a univariate unadjusted regression model with occurrence of endometrial malignancy as dependent variable. Subsequently, a multivariate logistic regression analysis was performed to test whether possible predictors remained significant. This adjusted analysis included all covariates that appeared to be associated ($p <$ 0.05) with the endpoint in the first analysis. Receiver operating characteristic (ROC) curve analysis was used to determine a cut-off value of transvaginal ultrasound score for an identification of endometrial malignancy.

**Results**

Average age of participants was 50.6 ± 3.42 years. The majority of the participants (66%) were pluripara. Average number of deliveries was 1.74 ± 0.75. Twenty women had history of spontaneous abortion, while 27% had planned abortion. Eighteen females in this sample had a sterility

problem. The average age of menarche age was 12.11 ± 1.60 years. Regular menstrual cycle was present for 31% patients. Twenty-eight females had hypertension, 13% had dysfunction of thyroid gland, while 8% had diabetes. Forty-three (43%) women included in this investigation were smokers. One-third of patients had an obesity problem. The distribution of initial diagnosis before transvaginal ultrasound was as follows: endometrial hyperplasia (43%), endometrial polyp (37%), and with a diagnosis of suspicion of carcinoma (7%). Problems with uterine bleeding during the examination were present in 52% of participants. Histopathological analysis showed that 21% patients had malign and 79% benign pH finding. According to the data illustrated in Figure 1, the values of transvaginal ultrasound score in this sample of perimenopausal females ranged from 4 to 13. In the group of women with benign histopathological findings, the average value of this score was 6.96 ± 1.85 (range 4-11), while in the group of women with malignant histopathological findings, the average value of this score was 10.38 ± 1.86 (range 7-13). The differences between transvaginal ultrasound score among these two subcohorts was statistically highly significant ($t$ = - 7.522; $p <$ 0.001). The "gray zone" of overlapping values in these two groups ranged between 7 and 11. Table 1 labeled "sensitivity and specificity" tabulates those values for each possible cut-off between benign and malignant histopathological findings. The best validity of transvaginal ultrasound score for detection of endometrial malignancy was observed with the value of 8, specifying a sensitivity of 0.857 and specificity of 0.785.

The predictors of endometrial malignancy that were identified using logistic regression models are illustrated in Table 2. The unadjusted models have revealed that prognostic value for occurrence of endometrial malignancy had following variables: spontaneous abortion, hypertension, obesity, and transvaginal ultrasound score. Furthermore, after testing for variable interaction and controlling the ef-

Table 2. — *Logistic regression models of predictors of endometrial malignancy in premenopausal women.*

|  | Unadjusted models | | | Adjusted model | | |
| --- | --- | --- | --- | --- | --- | --- |
|  | OR | 95% CI | *p* | OR | 95% CI | *p* |
| Age (years) | 1.07 | 0.92 – 1.24 | 0.348 |  |  |  |
| Menarche (years) | 1.04 | 0.77 – 1.40 | 0.795 |  |  |  |
| Parity | 0.48 | 0.18 – 1.28 | 0.143 |  |  |  |
| Spontaneous abortion | 8.56 | 2.84 – 25.76 | < 0.001 | 6.17 | 1.16 – 32.80 | 0.033 |
| Intentional abortion | 0.57 | 0.17 – 1.89 | 0.360 |  |  |  |
| Treated sterility | 3.09 | 1.02 – 9.36 | 0.046 |  |  |  |
| Menstrual cycle regularity | 1.16 | 0.40 – 3.34 | 0.79 |  |  |  |
| Hypertension | 5.25 | 1.89 – 14.61 | 0.001 | 4.09 | 0.75 – 22.42 | 0.105 |
| Thyroid disorders | 1.83 | 0.50 – 6.65 | 0.359 |  |  |  |
| Diabetes mellitus | 1.01 | 0.24 – 2.35 | 0.987 |  |  |  |
| Smoking | 2.06 | 0.78 – 5.47 | 0.145 |  |  |  |
| Obesity | 3.93 | 1.44 –10.71 | 0.007 | 2.41 | 0.47 – 12.34 | 0.292 |
| Endometrial hyperplasia in obs. | 0.45 | 0.16 – 1.29 | 0.139 |  |  |  |
| Endometrial polyps in obs. | 0.62 | 0.22 – 1.77 | 0.371 |  |  |  |
| Metrorrhagia | 1.30 | 0.49 – 3.43 | 0.596 |  |  |  |
| Transvaginal ultrasound score | 2.52 | 1.69– 3.75 | < 0.001 | 2.55 | 1.58 – 4.11 | < 0.001 |

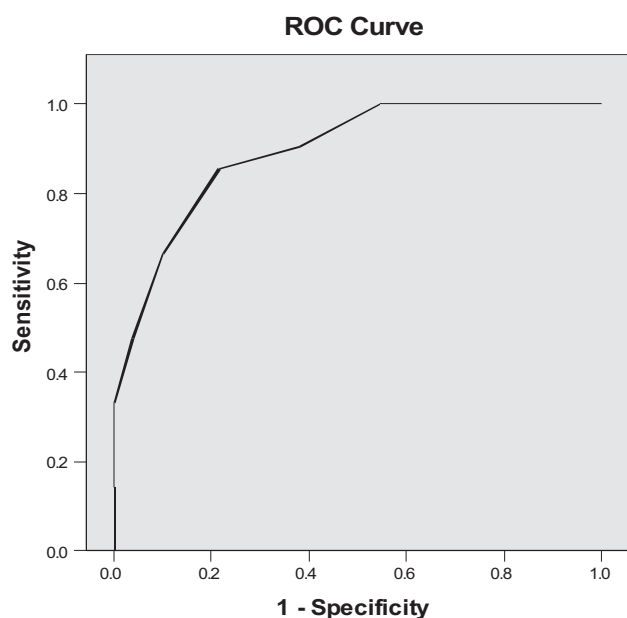OR: odds ratio; CI: confidence interval; bold value indicated statistical significance.



Figure 2. — ROC curve indicating effectiveness of transvaginal ultrasound score for a identification of endometrial malignancy.

vaginal ultrasound score, the risk for detection of endometrial malignancy scale increased by 2.52-fold (OR = 2.52, *p* = < 0.001). The area under a ROC curve quantified the overall ability of the test to discriminate between those individuals with the disease and those without the disease (Figure 2). A truly useless test (one no better at identifying true positives than flipping a coin) had an area of 0.5. A perfect test (one that has zero false positives and zero false negatives) has an area of 1.00. In this investigation the area under the curve was 0.896, indicating an excellent effectiveness of transvaginal ultrasound score for the identification of endometrial malignancy.

**Discussion**

In the present sample of perimenopausal women, 31% had regular cycles in the last six months, which was consistent with the facts regarding irregularities and abnormalities of the perimenopause cycle.

Twenty-eight females suffered from hypertension, which is consistent with the result obtained by Litta *et al.* [7]. Thirteen of participants suffered from a thyroid dysfunction and 8% of all participants had diabetes [8]. In the present study risk factors, cigarette smoking, and obesity confirmed that these are risk factors for endometrial cancer [9-11]. In 35 patients, endometrial polyps were confirmed, therefore the interventions were justified. Due to the possibility of a malignancy within a polyp, numerous experts believe that such a change ought to be removed. [12]. The majority (52%) of women in the present investigation had endometrial bleeding during examination which is in agreement with previous findings that during perimenopause, the risk of creation of lignities on endometrium increased with abnormal bleeding [13].

fect of potential confounders, the multivariate adjusted model demonstrated that independent prognostic value for detection of endometrial malignancy remained significant only for spontaneous abortion and transvaginal ultrasound score. Namely, this analysis showed that women with spontaneous abortion in medical history had six-fold greater chance to develop endometrial cancer compared to females without this spontaneous abortion in medical history (OR = 6.17, *p* = 0.033). Additionally, this predictive model also demonstrated that with each one-unit increase in trans-

The results from this study have been confirmed that the thickness of endometrium cannot be observed separately from other parameters which have been measured. This was also shown by the other studies where the ultrasound examination of the thickness of endometrium reached 80.5% of sensitivity, but was predicted to be low-specific 61% and with a dramatic decrease with asymptomatic patients [14, 15].

Appleton and Kupesic-Plavsic pointed out the necessity of a uterus examination before intervention, whether there is an endometrial biopsy or curettage in question. The ultrasound examination with colour Doppler enabled a detailed examination of the thickness, structure, and flow through the endometrium prior to intervention. They placed the cut-off of the thickness of endometrium at five mm and each patient was examined separately, depending on a lower or higher cancer risk, which is consistent with the present research [16].

In the study of Hee *et al.*, retrieved material via hysteroscopy after a suspicion of endometrial polyp and histopathology showed  benignity in 96.7%, pre-malignancy in 1.1%, and a malignity in 2.2%. In this survey, abnormal uterine bleeding and post-menopause were the only factors which were determined to be associated with a higher risk of malignancy, with an OR of 5.07 (95% CI, 2.25−11.41) and 3.41 (95% CI, 1.14−10.24), respectively [17]. Most authors agree that with the increase in the thickness of endometrium, the possibility of occurrence of malignancy increases as well, thus they consider a six-mm thickness of endometrium with women who have not had cycle within the last six months or with perimenopausal women to be hyperplasia.

Giannella *et al.* in their work aimed at discovering the adequate risk score for discovering an endometrial malignant with symptomatic post-menopausal women. They found that the best predictors of endometrial cancer were recurrent vaginal bleeding (OR = 2.96), the presence of hypertension (OR = 2.01) endometrial thickness > eight mm (OR = 1.31), and age > 65 years (OR = 1.11). These variables were used to create a risk-scoring model (RHEA risk-model) for the prediction of intrauterine malignancy, with an area under the curve of 0.878 (95% CI 0.842−0.908; $p <$ 0.01). At the best cut-off value (score $\geq$ 4), sensitivity and specificity were 87.5% and 80.1%, respectively [18].

Ultrasound has been necessary so far and all the possibilities of new technologies should be used in order to create a system for detecting patients with a potential malignant disease [19]. In the present sample of perimenopausal women, a transvaginal ultrasound examination was performed in each patient and each parameter of the ultrasound score was evaluated in order to receive a certain score. Regression analysis showed that this transvaginal ultrasound score has independent prognostic values for detection of endometrial malignancy. In the group of women with benign histopathological findings, the average value of this score was $6.96 \pm 1.85$ (range 4−11), while in the group of women with malignant histopathological findings the average value of this score was $10.38 \pm 1.86$ (range 7−13). The best validity of transvaginal ultrasound score for detection of endometrial malignancy is observed with a value of 8, specifying the sensitivity of 0.857 and specificity of 0.785. This finding pointed out that females with transvaginal ultrasound score more than 8 should be promptly submitted to an invasive diagnostics of fractional explorative curettage or hysteroscopy, while those with a score lower than 8 should be carefully followed and monitored. It has been well-recognised that there is no reliable tests or ultrasound indicator which could diagnose a pre-malignant or initial malignant change on the endometrium. It is often difficult to differentiate a benign change on the endometrium from a malignant and a gynaecologist requires assistance to triage patients. Incorporation of this transvaginal ultrasound score as a screening tool in detection of endometrial malignancy should reduce the number of unnecessary interventions. Angioli *et al.* have also shown that a score is needed to triage such patients, by publishing Risk of Endometrial Malignant ( REM) test by combining serum markers, clinical characteristics, and ultrasound values [20]. Their results, as in the present study, showed that such scoring systems are useful for triage of patients, reduction of the costs of diagnostics and treatment, and for more rapid diagnostics [20].

Kurjakand *et al.* monitored endometrial volume and Doppler criteria for malignancy on endometrium, including sub-endometrial halo, compactness, existence of intracavitary liquid, and neo-vascularisation, and have found that the volume with endometrial cancer amounts to $37.0 \pm 31.8$ ml, the volume with hyperplasia has medium value 7.82 ml, and that the volume with endometrial polyp is significantly high (mean $2.63 \pm 2.12$ ml) [21]. There are many studies in literature in which the development of nomograms led to successful applications in oncology and developing an accurate predictive nomogram of malignancy risk would be of great importance, helping to avoid over- or under-treatment of patients with endometrial cancer [22]. The introduction of such a scoring system for predicting endometrial cancer, further research, and usage of technological advancements in the world of cancer diagnostics are still necessary.

## Conclusion

Ultrasound in gynaecology is an entity which is developing, is accepting new challenges in examining gynaecological pathologies via new methods and modalities. The present study suggests that transvaginal ultrasound score could be applied as a prognostic marker for detection of endometrial cancer in perimenopausal women. These instruments, in addition to traditional measures of clinical outcome, provide additional information and could be a

part of a more comprehensive prediction of patient's prognosis. However, the authors would like to emphasize that, at present, these results are not generalizable and further studies with external validation are mandatory.

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